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Overview of Pharmacovigilance

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ABSTRACT

Clinical research is an essential component of medical advancement, focusing on understanding health and disease to enhance healthcare practices. This exploration encompasses clinical trials, classified into interventional studies and observational studies. Interventional studies, or clinical trials, involve assigning participants interventions to evaluate their effects on health outcomes. These interventions can range from drugs to surgical procedures or preventive care. Clinical trials progress through four phases, ensuring safety and efficacy before widespread implementation. The International Clinical Trials Registry Platform (ICTRP), a global initiative by WHO, facilitates comprehensive and accessible information on human clinical trials. ICTRP strives to enhance data accuracy, raise awareness about trial registration, and promote data utilization. This collaborative effort fosters transparency, benefiting not only researchers but also patients, families, and the broader healthcare community.

KEYWORDS: *Phase, Drug, Trial, Asthama, Clinical Trial, Treatment, Salubutamol, risk*

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INTRODUCTION

Medicines and vaccines have transformed the prevention and treatment of diseases. In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.

All medicines and vaccines undergo rigorous testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time. Certain side effects may only emerge once these products have been used by a heterogeneous population, including people with other concurrent diseases, and over a long period of time.

CLINICAL RESEARCH

Clinical trials:

Clinical research is medical research that studies people to understand health and disease. Clinical research helps improve the way doctors treat and prevent illness. Through clinical research, researchers learn:

- How the body works
- How illness develops in people, such as how diseases get better or worse over time
- How the body handles a possible treatment
- Which behaviors help people stay healthy and prevent illness, and which behaviors raise the chance of illness

The goal is to use science to improve people's health care and health over time. The participants who join and take part in clinical research studies may or may not get any benefit for themselves.

There are 2 main types of clinical research:

- Clinical trials, also called interventional studies.
- Observational studies.

Clinical trials (Intervention studies) research studies in which researchers assign participants to get one or more interventions to test what happens in people. Because of this, clinical trials are also called interventional studies.

Observational studies, are research studies in which researchers simply collect information (called data) from participants or look at data that was already collected.

Clinical trials are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes. People volunteer to take part in clinical trials to test medical interventions including drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments and preventive care.

There are 4 phases of biomedical clinical trials:

- Phase I studies usually test new drugs for the first time in a small group of people to evaluate a safe dosage range and identify side effects.
- Phase II studies test treatments that have been found to be safe in phase I but now need a larger group of human subjects to monitor for any adverse effects.
- Phase III studies are conducted on larger populations and in different regions and countries, and are often the step right before a new treatment is approved.
- Phase IV studies take place after country approval and there is a need for further testing in a wide population over a longer timeframe.

Understanding the basis of clinical trial phases will help researchers plan and implement clinical study protocols and, by doing so, improve the number of therapies coming to market for patient.

WHO's International Clinical Trials Registry Platform (ICTRP) links clinical trials registers globally in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others.

The ICTRP is a global initiative that aims to make information about all clinical trials involving humans publicly available. It also aims to:

- improve the comprehensiveness, completeness and accuracy of registered clinical trial data;
- communicate and raise awareness of the need to register clinical trials;
- ensure the accessibility of registered data;
- build capacity for clinical trial registration;
- encourage the utilization of registered data; and
- ensure the sustainability of the ICTRP.

Each phase has a different purpose:

- A Phase 1, trial tests an experimental drug or device on a small group of people (around 20 to 80) to judge its safety, including any side effects, and to test the amount (dosage).
- A Phase 2, trial includes more people (around 100 to 300) to help determine whether a drug is effective. This phase aims to obtain preliminary data on whether the drug or device works in people who have a certain disease or condition. These trials also continue to examine safety, including short-term side effects.
- A Phase 3, trial gathers additional information from several hundred to a few thousand people about safety and effectiveness, studying different populations and different dosages, and comparing the intervention with other drugs or treatment approaches. If the FDA agrees that the trial results support the intervention's use for a particular health condition, it will approve the experimental drug or device.
- A Phase 4, trial takes place after the FDA approves the drug or device. The treatment's effectiveness and safety are monitored in large, diverse populations. Sometimes, side effects may not become clear until more people have used the drug or device over a longer period of time.

Phase 0 trials:

The earliest trials of drugs in people are usually phase 1 trials. But your doctor might ask if you would like to join a phase 0 study. These studies aim to find out if a drug behaves in the way researchers expect it to from their laboratory studies.

Phase 0 studies usually only involve a small number of people and they only have a very small dose of a drug. The dose of the drug is too small to treat your cancer, but you are also less likely to have side effects.

Phase 0 trials aim to find out things such as:

- whether the drug reaches the cancer cells.
- what happens to the drug in the body.
- how cancer cells in the body respond to the drug.

Phase 1 trial:

Phase 1 is sometimes written as phase I. They are usually small trials, recruiting only a few patients. The trial may be open to people with any type of advanced cancer, usually those who have already had all other available treatments. Phase 1 trials aim to find out:

- how much of the drug is safe to give.
- what the side effects are.
- what happens to the drug in the body.
- if the treatment helps shrink the cancer. Patients are recruited very slowly onto phase 1 trials. So even though they don't recruit many people, they can take a long time to complete.

They are often dose escalation studies. This means that the first few patients that take part have a very

small dose of the drug. If all goes well, the next few people have a slightly higher dose. And so on until they find the best dose to give. The researchers monitor the side effects people have and how they feel.

In a phase 1 trial you may have lots of blood tests because the researchers look at how your body copes with and gets rid of the drug. They carefully record any side effect you may have and when you have them.

The main aim of phase 1 trials is to find out about doses and side effects. They need to do this first, before testing the potential new treatment to see if it works. Some people taking part may benefit from the new treatment, but many won't.

Phase 2 trials:
Phase 2 is sometimes written as phase II. Not all treatments tested in a phase 1 trial make it to a phase 2 trial.

These trials can be for people who all have the same type of cancer, or for people who have different types of cancer.

Phase 2 trials aim to find out:
- if the new treatment works well enough to be tested in a larger phase 3 trial.
- which types of cancer the treatment works for.
- more about side effects and how to manage them.

more about the best dose to give. These treatments have been tested in phase 1 trials, but you may still have side effects that the doctors don't know about. Treatments can affect people in different ways. Some people taking part may benefit from the new treatment, but some won't.

Phase 2 trials are usually larger than phase 1. There may be up to 100 or so people taking part. Sometimes in a phase 2 trial, a new treatment is compared with another treatment already in use, or with a dummy drug.

Some phase 2 trials are randomized. This means the researchers put the people taking part into treatment groups at random.

Phase 3 trials:
Phase 3 is sometimes written as phase III. These trials compare new treatments with the best currently available treatment (the standard treatment).

Phase 3 trials aim to find out:
- which treatment works better for a particular type of cancer.
- more about the side effects.
- a completely new treatment.
- different doses of the same treatment
- having the same treatment more, or less, often
- a new way of giving a standard treatment (radiotherapy for example).

Phase 3 trials usually involve many more patients than phase 1 or 2. This is because differences in success rates may be small. So, the trial needs many patients to be able to show the difference.

Sometimes phase 3 trials involve thousands of people in many different hospitals and even different countries. Most phase 3 trials are randomised. This means the people taking part are put into treatment groups at random. See our information about randomised trials.

Phase 4 trials:
Phase 4 is sometimes written as phase IV. These trials are done after a drug has been shown to work and has been licenced. Phase 4 trials aim to find out:
- more about the side effects including the rarer side effects and safety of the drug
- what the long term risks and benefits are
- how well the drug works when it's used more widely for people not included in the phase 3 trial.

Functions of Drug Controller General of India (DCGI) and Central Drugs Standard Control Organization (CDSCO):

Drug Controller General of India (DCGI):
DGCI is the central licensing authority for medical devices which fall under the Medical Device Rules 2017.

Parent Ministry:
CDSCO headed by Drug Controller General of India, functions under Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India.

DCGI is responsible for:

A. Establishment of standards relating to manufacture, sale, import and distribution of medicines in India.

B. Regulation of medical and pharmaceutical devices.

C. acts as an appellate authority in disputes related to the quality of medicine.

D. Preparation and maintenance of the national reference standard for medicines

E. Toensure the uniformity of the implementation of the Law on Medicines and Cosmetics.

Central Drugs Standard Control Organization (CDSCO):
It is the drug regulatory body of India headed by the Chief Drug Controller of India under the Ministry of

Health and Family Welfare. CDSCO under Director General of Health Services, Ministry of Health & Family Affairs, Govt. of India is the main regulatory body for drugs, medical devices and clinical trials in India. Headquartered in New Delhi, CDSCO has six zonal offices, seven sub-zonal offices, thirteen ports and seven laboratories across the country. CDSCO's mission is to ensure and improve public health by ensuring the safety, efficacy and quality of medicines, cosmetics and medical devices.

Headquarter:
New Delhi. It also has six zonal offices. Mandate of CDSCO: To bring out transparency, accountability, and uniformity in its services in order to ensure safety, efficacy, and quality of the medical product manufactured, imported, and distributed in the country.

Zonal Offices: The zonal offices are involved in GMP (good manufacturing practice) audits and inspection of manufacturing units of large volume parenteral, sera, vaccine and blood products.

The 6 zonal offices are in:
1. Mumbai,
2. Kolkata,
3. Chennai,
4. Ghaziabad,
5. Ahmedabad,
6. Hyderabad.

Sub-Zonal Offices: These centres co-ordinate with state drug control authorities under their jurisdiction for uniform standard of inspection and enforcement, 7 sub-zonal offices are located at.
1. Bengaluru,
2. Varanasi,
3. Goa,
4. Jammu,
5. Indore,
6. Guwahati,
7. Baddi.

Laboratories: The laboratories are responsible for quality control of drugs and cosmetics in the country. The laboratories are:
1. Central Drug Laboratory, Kolkata,
2. Central Drug Testing Laboratory, Mumbai,
3. Central Drug Testing Laboratory, Chennai,
4. Central Drug Laboratory, Kasauli,
5. Regional Drug Testing Laboratory, Guwahati,
6. Regional Testing Laboratory, Chandigarh,
7. Central Drug Testing Laboratory, Hyderabad.

Functions:
1. Approval of the New Drugs,
2. Approval and Conduct of the Clinical Trials,
3. Laying down the standards for Drugs,
4. Control over the quality of imported drugs in the country and
5. Coordination of the activities of State Drug Control Organizations by providing expert advice with a view of brings about uniformity in the enforcement of the Drugs and Cosmetics Act.
6. Registration of foreign manufacturers of drugs and medical devices whose products are to be imported into the country.
7. Grant of licenses to import drugs by Government hospitals or Medical Institutions for the use of their patients.
8. Recommend banning of drugs considered harmful or sub-therapeutic under section 26A drugs and Cosmetics Act.
9. License approving of Blood Banks, Vaccines, Low Volume Parenteral, r-DNA products and some Medical Devices
10. Banning of drugs and cosmetics.
11. Grant of test license, personal license and NOCs for export.
12. Testing of new drugs.
13. Oversight and market surveillance through inspectorate of centre over and above the state authority.
14. Participate in WHO GMP certification scheme.
15. Publish Indian Pharmacopoeia.
16. Monitoring adverse drug reactions. Laying down regulatory measures and amendments to D&C Act and Rules.(8)

Types of Regulatory Applications:

1. Investigational New Drug Application (INDA):
A pharmaceutical company can use the Investigational New Drug (IND) program to obtain approval to begin human clinical trials and send an experimental drug across national borders (often to clinical investigators before submitting a drug application). A New Drug Application (IND) must demonstrate that human trials of the new drug can begin. The IND application is also the means by which the sponsor moves into the phase of drug development known as clinical trials. Current federal law requires that an approved cooperative application (Clinical Investigators) be submitted before a drug can be transported or distributed interstate. Because the sponsor likely wants to send the investigational drug to investigators in multiple states, it must request an exemption from this legal requirement. An IND application is the means by which a sponsor receives a technical exemption from the FDA.(9,10)

Classification of IND:

- **Commercial:**

Permits sponsor to collect data on clinical safety and effectiveness needed for application for marketing in form of NDA.

➢ **Research (Non-commercial):**
Permits the sponsor to use drug in research to obtain advanced scientific knowledge of new drug. No plan to market the drug.(11)

Types of IND Applications:
1. Investigator IND application,
2. Emergency Use IND application,
3. Treatment IND application,
4. Screening IND application.

2. New Drug Application (NDA):
The regulation and control of new drugs in the United States was based on the New Drug Application (NDA) program. Since 1938, every new drug had an approved NDA before it was considered commercial in the United States. An NDA application is the means by which drug sponsors formally propose that the FDA approve a new drug for sale and marketing in the United States. An IND derived from animal and human clinical trials becomes part of the NDA.(11)

3. Abbreviated New Drug Application (ANDA):
1. "ANDA" means "New Drug Application". It contains information that, when Submitted to the FDA's Office of Generic Drugs, allows for review and final approval of generic drugs.
2. After approval, the applicant can manufacture and market generic drugs, provided that all aspects related to patent protection, safety, effectiveness, affordable alternative to the public.
3. Generic drug applications are called "abbreviated" because they usually do not need to include preclinical (animal) and clinical (human) data to demonstrate safety and efficacy. A generic drug is a drug comparable to an innovative drug in terms of dosage form, strength, method of administration, quality, action characteristics and purpose of use.

GOOD CLINICAL PRACTICES Good clinical practices:
Good clinical practice (GCP) is an
international quality standard, which governments can then transpose into regulations for clinical trials involving human subjects. GCP follows the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), and enforces tight guidelines on ethical aspects of clinical research.(12)

High standards are required in terms of comprehensive documentation for the clinical protocol, record keeping, training, and facilities, including computers and software. Quality assurance and inspections ensure that these standards are achieved. GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the investigational product are properly documented.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, registration and reporting of human trials. Adherence to this standard provides public assurance that the rights, safety and well-being of subjects are protected according to the principles of the Declaration of Helsinki and that clinical trials are reliable. The purpose of this ICH GCP guideline is to provide a common standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by regulatory authorities in these jurisdictions. The guide was developed taking into account the current good clinical practices of the European Union, Japan and the United States, as well as Australia, Canada, the Nordic countries and the World Health Organization (WHO). These guidelines must be followed when collecting clinical trial data for submission to regulatory authorities.

The principles of this guideline can be applied to other clinical trials that may affect human safety and well-being.(13)

ICH GUIDELINE:

ICH Code	Guideline title
Q1A	Stability testing of New Drug Substances and Products (Second Revision)
Q1A (R2)[2]	Stability testing of new drug substances and products[2]
Q1B	Stability testing: Photo stability testing of New Drug Substances and Products
Q1C	Stability testing of New Dosage Forms
Q1D	Bracketing and Matrixing Designs for stability testing of Drug Substances and Products
Q1E	Evaluation of stability data
Q1F	Stability data package for Registration Applications in Climatic Zones III and IV
Q5C	Stability testing of Biotechnological/Biological Products

Source: (ICH.org)

CONCEPT OF PHARMACOVIGILANCE
Pharmacovigilance:
Introduction to pharmacovigilance:
Medicines and vaccines have transformed the prevention and treatment of diseases. In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and / or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.(14)

All medicines and vaccines undergo rigorous testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time. Certain side effects may only

emerge once these products have been used by a heterogenous population, including people with other concurrent diseases, and over a long period of time.

The main goal of pharmacovigilance is thus to promote the safe and effective use of health products, in particular by providing timely information about the safety of health products to patients, health-care professionals, and the public.

Pharmacovigilance is therefore an activity contributing to the Pharmacovigilance supports safe and appropriate use of drugs. Spontaneous reporting of adverse drug reactions (ADRs) is an essential component of pharmacovigilance. However, there is significant underreporting of ADRs. Adverse drug reactions have become a major problem in developing countries. Knowledge of pharmacovigilance could form the basis for interventions aimed at improving reporting rates and decreasing ADRs. Detection of patients and maintaining public health. A new treatment goes through several phases.(15,16)

Objectives :

1. Improve patient care and safety in relation to the use of medicines and all medical and paramedical intervention
2. Improve public health and safety in relation to the use of medicines
3. Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use and
4. Promote understanding, education, and clinical training of pharmacovigilance and its effective communication to the public (17).

Pharmacovigilance Programme of India (PVPI):

The **Pharmacovigilance Programme of India** (**PvPI**) is an Indian government organization which identifies and responds to drug safety problems. Its activities include receiving reports of adverse drug detection and taking necessary action to remedy problems.

The **Pharmacovigilance Program of India (PvPI)** was launched with a broad objective to safeguard the health of people of India. Adverse drug Reactions (ADRs) are reported from all over the country to NCC-PvPI, which also works in collaboration with the global ADR monitoring centre (WHO-UMC), Sweden to contribute in the global ADRs database. NCC-PvPI monitors ADRs among Indian population and helps the regulatory authority of India (Central Drugs Standard Control Organization, CDSCO) in taking decisions for safe use of medicines.

The mission of PvPI is to safeguard the health of the Indian population by ensuring that the benefit of use of medicine outweighs the risks associated with its use. Since there exist considerable social and economic consequences of adverse drug reactions and the positive benefit/cost ratio of implementing appropriate risk management - there is a need to engage healthcare professionals and the public at large, in a well structured program to build synergies for monitoring adverse drug reactions in the country.(15)

The purpose of the PvPI is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public. The broadened patient safety scope of pharmacovigilance includes the detection of medicines of substandard quality as well as prescribing, dispensing and administration errors.

Counterfeiting, antimicrobial resistance, and the need for real time surveillance in mass vaccinations are other pharmacovigilance challenges which need to be addressed.

The **vision** of PvPI is to improve patient safety and welfare in Indian population by monitoring drug safety and thereby reducing the risk associated with use of medicines. The ultimate safety decisions on medicines may need considerations of comparative benefit/risk evaluations between products for similar indications.(16)

INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH) E2E GUIDELINES:

Elements of the non-clinical safety specification

The Safety Specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-approval period. This Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan. The Safety Specification can be built initially during the pre- marketing phase and, at the time approval is sought, it should reflect the status of issues that were being followed during development.

It is recommended that sponsors follow the structure of elements provided below when compiling the Safety Specification. The elements of the Safety Specification that are included are only a guide. The Safety Specification can include additional elements, depending on the nature of the product and its

development program. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

The focus of the Safety Specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered for inclusion(18)

Non-clinical:
Within the Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.)
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.)
- Drug interactions
- Other toxicity-related information or data.

If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

Identification and Evaluation of risks including drug-drug interactions and drug-food interactions:
Interactions between foods and drugs can have profound influence on the success of drug treatment and on the side effect profiles of many drugs. The interactions are not always detrimental to therapy, but can in some cases be used to improve drug absorption or to minimize adverse effects.

Design and Conduct of Observational Studies:
Carefully designed and conducted pharmacoepidemiological studies, specifically observational (non- interventional, non-experimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator "observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice."

Before the observational study that is part of a Pharmacovigilance Plan commences, a protocol should be finalised. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the Pharmacovigilance Plan. Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings.

It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology.

2. In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed.

The highest possible standards of professional conduct and confidentiality should always be maintained and any relevant national legislation on data protection followed.

SELECTION OF DRUGS CLASS

Selection of a drug class for pharmacovigilance study using different criteria (e.g. commercial availability, selling of drugs etc.) Profiling of selected drug class (e.g. mechanism of action, pharmacological effects, indications, adverse effects, drug interactions, contraindications

Selection of a drug class for pharmacovigilance study using different criteria (e.g. commercial availability, selling of drugs etc.)

Drug category: Anti-asthmatic.

DRUG CLASS: BRONCHODILATORS Asthma is a chronic lung disease affecting people of all ages. It is caused by inflammation and muscle tightening around the airways, which makes it harder to breathe.

Symptoms can include coughing, wheezing, shortness of breath and chest tightness. These symptoms can be mild or severe and can come and go over time.

Although asthma can be a serious condition, it can be managed with the right treatment. People with symptoms of asthma should speak to a health professional. People with under-treated asthma can suffer sleep disturbance, tiredness during the day, and poor concentration. Asthma sufferers and their families may miss school and work, with financial impact on the family and wider community. If symptoms are severe, people with asthma may need to receive emergency health care and they may be admitted to hospital for treatment and monitoring. In the most severe cases, asthma can lead to death.(18)

Symptoms
Symptoms of asthma can vary from person to person. Symptoms sometimes get significantly worse. This is

known as an asthma attack. Symptoms are often worse at night or during exercise.

Common symptoms of asthma include:

1. a persistent cough, especially at night
2. wheezing when exhaling and sometimes when inhaling
3. shortness of breath or difficulty breathing, sometimes even when resting
4. chest tightness, making it difficult to breathe deeply.

Some people will have worse symptoms when they have a cold or during changes in the weather. Other triggers can include dust, smoke, fumes, grass and tree pollen, animal fur and feathers, strong soaps and perfume.

Symptoms can be caused by other conditions as well. People with symptoms should talk to a healthcare provider.

Causes

Many factors have been linked to an increased risk of developing asthma, although it is often difficult to find a single, direct cause.

Asthma is more likely if other family members also have asthma – particularly a close relative, such as a parent or sibling.Asthma is more likely in people who have other allergic conditions, such as eczema and rhinitis (hay fever).

Urbanization is associated with increased asthma prevalence, probably due to multiple lifestyle factors.

Events in early life affect the developing lungs and can increase the risk of asthma. These include low birth weight, prematurity, exposure to tobacco smoke and other sources of air pollution, as well as viral respiratory infections.

Exposure to a range of environmental allergens and irritants are also thought to increase the risk of asthma, including indoor and outdoor air pollution, house dust mites, moulds, and occupational exposure to chemicals, fumes or dust. Children and adults who are overweight or obese are at a greater risk of asthma.(18)

Treatment

Asthma cannot be cured but there are several treatments available. The most common treatment is to use an inhaler, which delivers medication directly to the lungs.

Inhalers can help control the disease and enable people with asthma to enjoy a normal, active life.

There are two main types of inhaler:

1. Bronchodilators (such as salbutamol), that open the air passages and relieve symptoms
2. Steroids (such as beclometasone) that reduce inflammation in the air passages, which improves asthma symptoms and reduces the risk of severe asthma attacks and death.

Report scope	Details
Market size by 2030	USD 26.01 billion
Growth rate from 2022 to 2030	CAGR of 2.6%
Largest market	North America, Europe
Fastest Growing Region	Asia Pacific
Companies Covered	AstraZeneca, Teva Pharmaceutices Industries Ltd, GlaxoSmithKline plc, Roche Holding AG/Novartis AG

The global asthma treatment market size stood at USD 18.08 billion in 2019 and is projected to reach USD 26.01 billion by 2030, exhibiting a CAGR of 4.5% during the forecast period.

Profiling of selected drug class (e.g. mechanism of action, pharmacological effects, indications, adverse effects, drug interactions, contraindications)

DRUG CLASS:
BRONCHODILATORS DRUG:
SALBUTAMOL

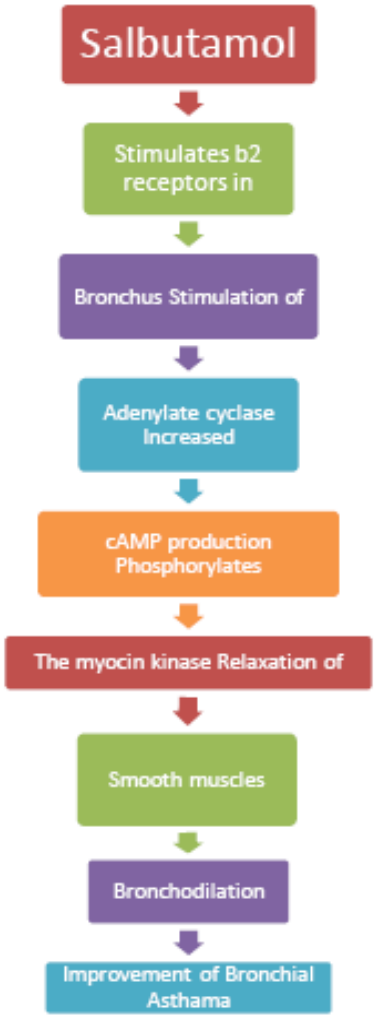
Salbutamol is a beta-2 adrenergic receptor agonist used to treat asthma, bronchitis, COPD, as well as prevent exercise induced bronchospasms.

Salbutamol, also known as albuterol and sold under the brand name Ventolin among others, is a medication that opens up the medium and large airways in the lungs.[19] It is a short-acting β2 adrenergic receptor agonist which works by causing relaxation of airway smooth muscle.It is used to treat asthma, including asthma attacks and exercise-

induced bronchoconstriction, as well as chronic obstructive pulmonary disease (COPD).[19] Salbutamol is a short-acting, selective beta2-adrenergic receptor agonist used in the treatment of asthma and COPD. It is 29 times more selective for beta2 receptors than beta1 receptors giving it higher specificity for pulmonary beta receptors versus beta1-adrenergic receptors located in the heart.

Mechanism of Action:

Directly binds to airway β2 adrenoceptors, stimulating smooth muscle relaxation and bronchodilation through induction of cAMP with resulting phosphorylation of muscle regulatory proteins and modification of cellular calcium concentration.



Pharmacological Effect:

Salbutamol is selective β2 receptors, which are the predominant receptors on the bronchial smooth muscles. Activation of these receptors causes adenylyl cyclase to convert ATP to cAMP, beginning the signalling cascade that ends with the inhibition of myosin phosphorylation and lowering the intracellular concentration of calcium ions (myosin phosphorylation and calcium ions are necessary for muscle contractions). The increase in cAMP also inhibits inflammatory cells in the airway, such as basophils, eosinophils, and most especially mast cells, from releasing inflammatory mediators and cytokines. Salbutamol and other β2 receptor agonists also increase the conductance of channels sensitive to calcium and potassium ions, leading to hyperpolarization and relaxation of bronchial smooth muscles.[20]

Indications: Salbutamol is indicated for the symptomatic relief and prevention of bronchospasm due to bronchial asthma, chronic bronchitis, reversible obstructive airway disease, and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor, and/or the acute prophylaxis against exercise-induced bronchospasm and other stimuli known to induce bronchospasm.

Adverse Effect:

- fine tremor,
- anxiety,
- headache,
- muscle cramps,
- mouth, and palpitation.

Other symptoms may include tachycardia, arrhythmia, flushing of the skin, myocardial ischemia (rare), and disturbances of sleep and behaviour.[21]

Drug Interactions:

DRUGS	INTERACTIONS
Abacavir	Salbutamol may decrease the excretion rate of Abacavir which could result in a higher serum level.
Acebutolol	The therapeutic efficacy of Salbutamol can be decreased when used in combination with Acebutolol.
Aceclofenac	The risk or severity of hypertension can be increased when Salbutamol is combined with Aceclofenac.
Acemetacin	The risk or severity of hypertension can be increased when Salbutamol is combined with Acemetacin.
Acetaminophen	Acetaminophen may decrease the excretion rate of Salbutamol which could result in a higher serum level.
Acetazolamide	Acetazolamide may increase the excretion rate of Salbutamol which could result in a lower serum level and potentially a reduction in efficacy.

Acetylsalicylic acid	The risk or severity of hypertension can be increased when Acetylsalicylic acidis combined with Salbutamol.
Aclidinium	Salbutamol may decrease the excretion rate of Aclidinium which could result in a higher serum level.
Acrivastine	The risk or severity of QTc prolongation can be increased when Salbutamol is combined with Acrivastine.
Acyclovir	Acyclovir may decrease the excretion rate of Salbutamol which could result in a higher serum level.

Contraindications:
Contraindicated in patients with high blood pressure during preganancy, uterine infection, miscarriage, heart disease, and hypersensitivity**.**

SELECTION OF DRUG:
Identification of most widely prescribed drug from a selected class (consumption report) by approaching pharmacy stores, company representatives and pharma companies web portal.)

Types of bronchodilators are available to treat asthma:
There are 3 types of bronchodilators used for treating asthma;(21)

1. Beta-adrenergic bronchodilators
2. Anticholinergic bronchodilator
3. Xanthine derivative

1. Beta-adrenergic bronchodilators
Beta-adrenergic bronchodilators relieve reversible bronchospasm by relaxing the smooth muscles of the bronchi. These agents act as bronchodilators and are used to treat bronchospasm in acute asthmatic episodes and to prevent bronchospasm associated with exercise-induced asthma or nocturnal asthma.

The 3 most widely used bronchodilators are: beta-2 agonists – like salbutamol, salmeterol, formoterol and vilanterol.

2. Anticholinergic bronchodilator
Anticholinergics (also known as antimuscarinics) are mainly used to treat COPD, but a few can also be used for asthma. They're usually taken using an inhaler, but may be nebulised to treat sudden and severe symptoms. Anticholinergics cause the airways to widen by blocking the cholinergic nerves.

Anticholinergics – like ipratropium, tiotropium, aclidinium and glycopyrronium.

3. Xanthine derivative
The xanthine derivatives are agents that resemble natural occurring xanthines such as caffeine, theobromine and methylxanthines. These are plant alkaloids and components of coffee, tea and chocolate. The major pharmacologic actions of the xanthines are inhibition of tissue phosphodiesterases which increases cellular cyclic AMP levels by inhibition of its breakdown and metabolism. The xanthines also have other activities mediated by their effects on different tissue phosphodiesterases including inhibition of platelet function and arterial vasodilation. These activities have potential use in preventing arterial thrombosis and thus prevention of myocardial infarction and stroke.The xanthines have many minor side effects (anxiety, nervousness, tremor, headache, dizziness) but are largely well tolerated in the doses used to treat asthma and chronic bronchitis. The xanthines are very rare causes of drug induced liver injury, most instances being mild and due to a hypersensitivity reaction or due to hepatic ischemia associated with overdose.(21)

Drug Class: Antiasthmatic Agents
Drugs in the Subclass, Xanthine Derivatives:
Theophylline, Pentoxifylline, Caffeine

List of short-acting and long-acting bronchodilators, anticholinergic bronchodilators, and xanthine derivatives:-

1. Short-acting beta adrenergic bronchodilator inhalers available in the US.

A. Albuterol (salbutamol)
Brand names: AccuNeb, Proair HFA, Proventil HFA, Ventolin HFA.

B. Levalbuterol
Brand names: Xopenex, Xopenex HFA.

C. Epinephrine injection
Brand names: Adrenaclick, Adernalin Auvi-Q, Epipen.

2. Long-acting beta adrenergic bronchodilators asthma inhaler are available in the US.

A. Salmeterol (fluticasone)
Brand names: Advair Diskus, AirDuo RespiClick.

B. Formoterol (budesonide)
Brand names: Atock, Atimos/Atimos Modulite, Fostair, Oxis.

3. Anti cholinergic bronchodilators are available in the US.

A. Ipratropium Bromide
Brand names: Atrovent.

B. Tiotropium Bromide
Brand names: Aerotrop, Aerotrop-F.

4. Examples of xanthine derivatives available in the US.

- Theophylline

Brand names: Theo 24, Elixophyllin.

IDENTIFICATION OF ADVERS EFFECTS OF A SELECTED DRUG.

Identification of adverse effect of selected drug using different search engines (e.g. Medscape .com, drugs.com, rxlist.com, etc.)

Salbutamol is safe and effective medicine, though like all other medicines, it does come with some side effects. Most common side effects of salbutamol include:

1. Feeling of shakeiness
2. Increased heartrate
3. Headaches
4. Cramps

The main side effects of beta-2 agonists like salbutamol include:

1. Trembling, particularly in the hands.
2. Nervous tension.
3. Headaches.
4. Suddenly noticeable heartbeats.
5. Muscles cramps.
6. A cough.
7. Nausea and vomiting.
8. Diarrhoea.

Conclusion

In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem. All medicines and vaccines undergo rigorous testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time. Clinical research is medical research that studies people to understand health and disease. Clinical research helps improve the way doctors treat and prevent illness. The goal is to use science to improve people's health care and health over time. Clinical trials (Intervention studies) research studies in which researchers assign participants to get one or more interventions to test what happens in people. Because of this, clinical trials are also called interventional studies. Clinical trials are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes. The ICTRP is a global initiative that aims to make information about all clinical trials involving humans publicly available. This phase aims to obtain preliminary data on whether the drug or device works in people who have a certain disease or condition.

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